

What I claim is :

1. A multilayered biocompatible structure comprising:  
a biopolymer membrane; and  
a biopolymer product in contact with the biopolymer membrane;  
wherein the biopolymer membrane in its substantially dry form has a thickness equal to or less than about 75 microns, a solvent content less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns.
- 5 2. The structure of claim 1 wherein the biopolymer membrane comprises a blend of a biomaterial and thrombin.
- 10 3. The structure of claim 2 wherein the biomaterial is autologous.
- 15 4. The structure of claim 3 wherein the biomaterial is selected from the group consisting of fibrin, fibrinogen, chondroitin-4 sulfate, dermatan sulfate, keratan sulfate, hyaluronic acid, chitosan, chitin, alginate, laminin, elastin, fibronectin, collagen, proteoglycan, glycosaminoglycan, and mixtures thereof
- 20 5. The structure of claim 1 wherein the biopolymer product comprises a blend of a biomaterial and thrombin.
- 25 6. The structure of claim 5 wherein the biomaterial is autologous.
7. The structure of claim 6 wherein the biomaterial is selected from the group consisting of fibrin, fibrinogen, chondroitin-4 sulfate, dermatan sulfate, keratan sulfate, hyaluronic acid, chitosan, chitin, alginate, laminin, elastin, fibronectin, collagen, proteoglycan, glycosaminoglycan, and mixtures thereof
- 30 8. The structure of claim 1 wherein the structure further comprises an additive mixed with the biopolymer membrane or the biopolymer product.
9. The structure of claim 8 wherein the additive is selected from the group consisting of processing aids, a radioactive marker, a calcium containing compound, an antibody, an antimicrobial agent, an agent for improving the biocompatibility of the structure, proteins, an anticoagulant, an anti-inflammatory compound, a compound reducing graft rejection, any living cell, cell growth inhibitors, agents stimulating endothelial cells, antibiotics, antiseptics,

analgesics, antineoplastics, polypeptides, protease inhibitors, vitamins, cytokine, cytotoxins, minerals, proteins, interferons, hormones, polysaccharides, genetic materials, proteins promoting or stimulating the growth and/or attachment of endothelial cells on the cross-linked biopolymer, growth factors, cell growth factors, growth factors for heparin bond, tannic acid, nerve growth

- 5 factor, neurotrophic factor (NTFs), neurotrophin 3 (NT3), brain derived NTF (BDNTF), ciliary NTF (CNTF), substances against cholesterol, pain killers, collagen, osteoblasts, chondroblasts, chondrocytes, osteoclasts, hematopoietic cells, stromal cells, osteoprogenitor cells, keratinocytes cells, anti coagulants, poly DL lactate, alginate, recombinant material, triglycerides, fatty acids, C<sub>12</sub>-C<sub>24</sub> fatty acids, collagen, any pharmaceutical agent, activable factor VII, activable factor IX, 10 activable factor X, activable factor XI, activable plasmin, photoactivatable t-PA, photoactivatable urokinase, taxol, cytostatic agent, antigenic agent, plasminogen, compounds activating the conversion of plasminogen into plasmin, compounds inhibiting the conversion of plasminogen in plasmin, and mixtures thereof.

- 15 10. The structure of claim 9 wherein the processing aid is a cryoprotectant.
11. The structure of claim 10 wherein the cryoprotectant is glycerol, dimethyl sulfoxide, or trehalose.
- 20 12. The structure of claim 9 wherein the radioactive marker is Technitium-99-m-HDP or an iodine isotope.
13. The structure of claim 9 wherein the substances against cholesterol are statins or stanols.
- 25 14. The structure of claim 9 wherein the pharmaceutical agent is selected from the group consisting of antibiotics, antiseptics, analgesics, and antineoplastics.
15. The structure of claim 9 wherein the compound that activates the conversion of plasminogen into plasmin is selected from the group consisting of t-PA, u-KA, su-PA, and 30 streptokinase.
16. The structure of claim 9 wherein the compound that inhibits the conversion of plasminogen in plasmin is selected from the group consisting of aprotinin, tranexamic acid, a2-antiplasmins, a2-macroglobulins, a2-antitrypsin, antithrombin, antistreptokinase, aminocapronic acid, tranexamic acid, C1-esterase inhibitor, and anti-urokinase.
- 35 17. The structure of claim 1 wherein the biopolymer membrane is cross-linked.

18. The structure of claim 1 wherein the biopolymer membrane is sterilized.
19. The structure of claim 2 wherein the thrombin is natural, recombinant, or a mixture thereof.
- 5 20. The structure of claim 5 wherein the thrombin is natural, recombinant, or a mixture thereof.
21. The structure of claim 2 wherein the thrombin is activatable.
- 10 22. The structure of claim 5 wherein the thrombin is activatable.
23. The structure of claim 1 wherein the thickness of the biopolymer membrane is equal to or less than about 45 microns.
- 15 24. The structure of claim 1 wherein the maximum pore size of biopolymer membrane is about 10 microns.
25. The structure of claim 1 wherein the maximum pore size of biopolymer membrane is about 5 microns.
- 20 26. The structure of claim 1 wherein the maximum pore size of biopolymer membrane is about 1 micron.
- 25 27. The structure of claim 1 wherein the maximum pore size of biopolymer membrane is about 0.10 micron.
- 30 28. The structure of claim 1 wherein the maximum pore size of biopolymer membrane is about 0.01 micron.
29. A multilayered biocompatible structure comprising:  
a first blend of a biomaterial and thrombin defining a biopolymer membrane;  
a second blend of a biomaterial and thrombin defining a biopolymer product;  
wherein the biopolymer membrane contacts the biopolymer product; and  
35 wherein the biopolymer membrane in its substantially dry form has a thickness equal to or less than about 75 microns, a solvent content less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns.

30. The multilayered biocompatible structure of claim 29 wherein the biomaterial of the first blend is fibrinogen.

31. The multilayered biocompatible structure of claim 29 wherein the thickness of the 5 biopolymer membrane is equal to or less than about 45 microns.

32. A biopolymer membrane comprising:

a blend of a biomaterial and thrombin, characterized in that the membrane in its substantially dry form has a thickness equal to or less than about 75 microns, a solvent content 10 less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns.

33. The biopolymer membrane of claim 32 wherein the biomaterial is fibrinogen.

15 34. The biopolymer membrane of claim 32 wherein the thickness is equal to or less than about 45 microns.

35. The biopolymer membrane of claim 32 wherein the maximum pore size is about 10 20 microns.

20 36. The biopolymer membrane of claim 32 wherein the maximum pore size is about 1 micron.

37. The biopolymer membrane of claim 34 wherein the maximum pore size is about 1 25 micron.

38. A multilayered biopolymer membrane comprising:

a first biopolymer membrane having has a thickness equal to or less than about 75 30 microns, a solvent content less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns; and

a second biopolymer membrane having a thickness equal to or less than about 45 35 microns, a solvent content less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 5 microns; and

wherein the first biopolymer membrane contacts the second biopolymer membrane.

39. An artificial skin comprising:

a blend of thrombin and fibrinogen defining a biopolymer membrane in its substantially dry form having a thickness equal to or less than about 75 microns, a solvent content less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns;

5 a first set of cells selected from the group consisting of fibroblast cells, endothelial cells, and a mixture thereof, wherein the first set of cells contact the biopolymer membrane; and

a second set of cells selected from the group consisting of epithelial cells, keratinocyte cells, and a mixture thereof, wherein the second set of cells contact the biopolymer membrane.

10 40. The artificial skin of claim 39 wherein the thickness of the biopolymer membrane is equal to or less than about 45 microns.

41. A process for forming a biopolymer membrane comprising:

mixing a biomaterial and thrombin in a solvent to define a gel;

drying the gel to define a sponge having a solvent content;

15 adjusting the solvent content of the sponge so that the sponge is substantially filled with the solvent; and

compressing the sponge to define a biopolymer membrane in its substantially dry form having a thickness less than about 75 microns and a solvent content less than about 5% by weight of the membrane, characterized in that the membrane has a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns.

42. The process of claim 41 wherein the biomaterial is autologous.

25 43. The process of claim 41 wherein the biomaterial is selected from the group consisting of fibrin, fibrinogen, chondroitin-4 sulfate, dermatan sulfate, keratan sulfate, hyaluronic acid, chitosan, chitin, alginate, laminin, elastin, fibronectin, collagen, proteoglycan, glycosaminoglycan, and mixtures thereof.

30 44. The process of claim 41 wherein the mixing is simultaneous or sequential.

45. The process of claim 41 wherein the compressing comprises at least two compressions.

35 46. The process of claim 41 wherein the drying is carried out by lyophilization, osmosis, centrifugation, compression, or a mixture thereof.

47. The process of claim 41 further comprising washing the biopolymer membrane.

48. The process of claim 41 wherein the thrombin is natural, recombinant, or a mixture thereof.

5 49. The process of claim 41 wherein the thrombin is activatable.

50. The process of claim 49 further comprising activating the thrombin.

51. The process of claim 50 wherein the activating is carried out by photoactivation or  
10 radiation.

52. The process of claim 41 further comprising adding an additive selected from the group consisting of processing aids, a radioactive marker, a calcium containing compound, an antibody, an antimicrobial agent, an agent for improving the biocompatibility of the structure, proteins, an anticoagulant, an anti-inflammatory compound, a compound reducing graft rejection, any living cell, cell growth inhibitors, agents stimulating endothelial cells, antibiotics, antiseptics, analgesics, antineoplastics, polypeptides, protease inhibitors, vitamins, cytokine, cytotoxins, minerals, proteins, interferons, hormones, polysaccharides, genetic materials, proteins promoting or stimulating the growth and/or attachment of endothelial cells on the cross-linked biopolymer, growth factors, cell growth factors, growth factors for heparin bond, tannic acid, nerve growth factor, neurotrophic factor (NTFs), neurotrophin 3 (NT3), brain derived NTF (BDNTF), ciliary NTF (CNTF), substances against cholesterol, pain killers, collagen, osteoblasts, chondroblasts, chondrocytes, osteoclasts, hematopoietic cells, stromal cells, osteoprogenitor cells, keratinocytes cells, anti coagulants, poly DL lactate, alginate, recombinant material, triglycerides, fatty acids, C<sub>12</sub>-C<sub>24</sub> fatty acids, collagen, any pharmaceutical agent, activable factor VII, activable factor IX, activable factor X, activable factor XI, activable plasmin, photoactivatable t-PA, photoactivatable urokinase, taxol, cytostatic agent, antigenic agent, plasminogen, compounds activating the conversion of plasminogen into plasmin, compounds inhibiting the conversion of plasminogen in plasmin, and mixtures thereof.

30 53. The process of claim 41 further comprising sterilizing the biopolymer membrane.

54. The process of claim 53 wherein the sterilizing agent is a physical agent or a chemical agent.

35 55. The process of claim 54 wherein the physical agent is selected from the group consisting of heat, radio frequency, gamma radiation, ion-beam, and electron beam radiation.

56. The process of claim 54 wherein the chemical agent is ethylene oxide.
57. The process of claim 41 further comprising drying the membrane.
- 5 58. The process of claim 41 further comprising cross-linking the biopolymer membrane.
59. The process of claim 58 wherein the cross-linking is effectuated with a cross-linking agent selected from the group consisting of aldehydes, diimides, enzymes, tri-hydroxybenzene carboxylic acids, and mixtures thereof.
- 10 60. The process of claim 59 wherein the tri-hydroxybenzene carboxylic acid is tannic acid.
61. The process of claim 59 wherein the aldehyde is formaldehyde or glutaraldehyde.
- 15 62. The process of claim 59 wherein the enzyme is factor XIII.
63. The process of claim 41 wherein the solvent is aqueous, organic, or a mixture thereof.
- 20 64. The process of claim 63 wherein the organic solvent is selected from the group consisting of cremophor, polyethyleneglycol, polysorbate.
65. The process of claim 41 further comprising stretching the biopolymer membrane.
- 25 66. The process of claim 41 further comprising associating the biopolymer membrane to a lattice.
67. A process for forming a multilayer biopolymer membrane comprising:  
providing a first biopolymer membrane in its substantially dry form having a thickness less than about 75 microns, a solvent content less than about 5% by weight of the membrane, a 30 radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a maximum pore size of about 20 microns;  
providing a second biopolymer membrane in its substantially dry form having a thickness less than about 75 microns, a solvent content less than about 5% by weight of the membrane, a radius of curvature of less than about 5 centimeters, a density greater than about 1 g/cm<sup>3</sup>, and a 35 maximum pore size of about 20 microns; and  
contacting the first biopolymer membrane to the second biopolymer membrane to define a multilayer biopolymer membrane.

TODAY'S DATE: 7/25/01

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68. The process of claim 67 wherein the first and second biopolymer membranes are of a different composition.

69. The process of claim 67 wherein the first and second biopolymer membranes each 5 comprise a biomaterial selected from the group consisting of fibrin, fibrinogen, chondroitin-4 sulfate, dermatan sulfate, keratan sulfate, hyaluronic acid, chitosan, chitin, alginate, laminin, elastin, fibronectin, collagen, proteoglycan, glycosaminoglycan, albumin, globulins, and mixtures thereof.

10 70. The process of claim 67 wherein the first and second biopolymer membranes each have a thickness that is different from the other.

71. The process of claim 67 wherein the thickness of the first biopolymer membrane is equal to or less than about 45 microns.

15 72. The process of claim 67 wherein the thickness of the second biopolymer membrane is equal to or less than about 45 microns.

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